

Dietary Treatment of Eosinophilic Esophagitis

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Introduction

Eosinophilic esophagitis (EoE) is an immune-mediated chronic inflammatory disorder that, in most children and many adults, is triggered by food antigens. In 1995 Kelly et al first described EoE in children and also demonstrated that clinical symptoms and eosinophilic esophageal inflammation was reversed with exclusive amino acid-based

elemental diet and exclusion of all food antigens.¹ The authors also identified specific food antigens including cow's milk, soy, wheat, egg and peanuts as potential proteins that induced the esophageal inflammation. These initial important observations from that first pediatric study form the basis of the different dietary approaches currently offered to treat EoE.

The goals of treatment in EoE, as for most other chronic disorders, include: 1) resolution of clinical symptoms, 2) maintenance of remission or prevention of disease relapse 3) prevention of complications such as fibrosis and strictures by maintaining histological remission 4) prevention of iatrogenic treatment related adverse reactions such as nutritional deficiencies as in dietary treatment and 5) maintenance of quality of life (QOL).

The dietary approach is based on the hypothesis that food antigens trigger eosinophilic inflammation and clinical along with histological remission can be induced by identifying and excluding the causative food antigens. It is believed that eliminating causative food antigens targets the cause and thus induces long-term remission. There are no prospective controlled double-blind studies assessing and demonstrating the efficacy of the different dietary approaches. The current recommendation for treatment of EoE with diet are based on a number of retrospective and observational studies.³⁻⁷ The available dietary approaches include: 1) elemental diet with an amino acid-based complete liquid formulation,^{1,3-5} 2) directed elimination diet based on the results of allergy testing⁶ and 3) standard or non-directed elimination diet where a number of common food antigens

are excluded from the diet.⁴ The type of treatment selected should be individualized and tailored to the needs of the patient and depend on the presence or lack of anaphylactic food allergies, the age of the child and the comfort and acceptance of the elimination diet by the family. Outcomes of all the different successful as well as unsuccessful dietary approaches are summarized in **Table1**.

Elemental Diet

Crystalline amino acid-based (exclusive) elemental diet was first successfully used to treat ten children with gastroesophageal reflux disease (GERD)-like symptoms resistant to acid suppression.¹ Clinical and histological remission occurred with introduction of exclusive amino acid-based formula in lieu of regular diet. Subsequent controlled reintroduction of solid foods resulted in recurrence of gastrointestinal symptoms specific to individual foods. A clear link between food allergy and esophageal injury was established in these patients.¹ Since this seminal publication by Kelly et al, two series of 172 and 25 cases reported a remission rate of 96% and 88% respectively in children treated with elemental diet (Neocate, Neocate EO28, Neocate 1+, SHS International, Liverpool, UK; or Elecare, Ross Pediatrics, Abbott Laboratories, Abbott Park, Illinois).³

⁴ This treatment outcome was achieved without any reported complications. The likelihood of achieving mucosal healing has been shown to be higher with this modality than other dietary interventions or with corticosteroids. The added advantages are the much lower residual eosinophil counts and thus almost complete remission with elemental diet. The disadvantage of this approach is the poor taste, patient compliance and impaired QOL due to elimination of regular foods. This limits ability to ingest it

orally and many of these children require either nasogastric or gastrostomy tubes to deliver adequate nutrients. The tube placement is also a source of patient discomfort and parental distress. Limiting a child to an exclusive elemental diet restricts the child's participation in social activities since many childhood activities involve food which can lead to impaired QOL. Elemental formulas are expensive and not always covered by most traditional insurance plans thereby placing significant financial and social burden on the families. There may also be additional costs related to tubes, pumps, bags and other supplies. Several states are covering or working towards providing coverage for the elemental formulas for EoE, but it continues to be a struggle for most families to get reimbursement for the cost of these formulations.

Once histological remission is established, as demonstrated with repeat endoscopy performed 4-6 weeks after exclusive elemental diet, food reintroduction is initiated beginning with the least allergenic foods from vegetable or fruit groups; a single food is introduced every 5-7 days, followed by a single food from within the grain, meats and nuts groups as outlined by Markowitz et al.⁵ In this algorithm the most allergic food group which includes foods such as cow's milk, soy, wheat, egg, chicken and corn are the last foods reintroduced. Single foods from a specific food group labeled from A to D as shown in **Table 2** are reintroduced in the diet every 5-7 days.⁸ Following successful reintroduction of all foods in one food group, endoscopic esophageal biopsies are performed to demonstrate continuing remission before introducing the next single food from the next food group. However if the patient is symptomatic following ingestion of

any given food, that food is excluded from the diet and the patient proceeds to the next food in that group once the symptoms have resolved.

Directed Elimination Diets Based on Results of Allergy Testing

Children treated with elimination diets based only on radioallergosorbent test (RAST) and/or skin prick test (SPT) results have failed to demonstrate clinical and histological remission.^{9, 10} In a prospective study in which adults were treated with standard elimination diet the predictive value of SPT for causal foods was only 22% in subjects.⁷ RAST testing and SPT alone or together fail to correctly identify foods causing esophageal inflammation in most patients. However when patients underwent both skin prick and atopic patch testing (APT) and were treated with an elimination diet based on the results of a combination of SPT and APT to common foods 78% demonstrated significant clinical and histological remission.⁶ Patients in this series underwent testing to common foods including meats (chicken, turkey, beef and pork), vegetables (peas, string beans, squash, sweet potatoes, potatoes and carrots), fruits (apples, pears and peaches), and grains (wheat, rice, rye, oats, barley and corn). Patients were also tested to milk protein, soy, eggs and peanuts. Milk, soy, wheat, chicken and beef were the foods most frequently identified by both APT and SPT. Of the 146 children treated with an elimination diet based on the results of both APT and SPT 112 (78%) responded with both clinical and histological improvement. Within this group 39 subjects were allergic to specific foods including milk, egg, soy and beef. Patch skin test lacks standardization for food allergies and is currently a research tool awaiting results of further studies to validate it.¹¹

Standard Elimination Diet

The advantage of standard or non-directed elimination diet, as also in the case of elemental diet, is that it does not require allergy testing to determine foods for elimination from the diet. In a retrospective study, six-food elimination diet (SFED) was utilized to treat a cohort of 35 children.⁴ Cow's milk protein, soy, wheat, egg, peanut/tree nut, fish and shellfish were the only foods excluded from the diet while all other solid foods were allowed. Twenty six (74%) children experienced significant clinical and histological improvement (esophageal eosinophil count $\leq 10/\text{HPF}$). There was complete mucosal healing with 0-1 eosinophil/hpf documented in esophageal biopsies in 7 of these 26 (27%) children. Complete histological remission induced by elimination diet is shown in **Figure 1**. This treatment approach has since been validated by a recent prospective study in which 78% of adults treated with SFED demonstrated histological improvement.⁷ The primary advantage of elimination diet over exclusive elemental diet is that it allows intake of a variety of table foods including meats, grains, fruits, vegetables, and legumes compared to a single nutrient source taken orally or via a tube. In situations where allergy testing is not easily accessible, and where elemental diet is not a consideration, this approach is the dietary treatment of choice. In addition this diet is not a significant drain on the families' budget.

Once clinical and histological remission with SFED is achieved, single food reintroduction in the diet is begun. Patients are evaluated after 4-6 weeks of new food re-introduction by endoscopy with esophageal biopsy. The next food is re-introduced after the histology establishes remission. **Figure 2** demonstrates abnormal endoscopic

appearance of the esophagus before treatment, normalization in response to dietary intervention with SFED, and recurrence with edema, swelling and exudate after challenge with wheat which had induced recurrence of symptoms. In a cohort of 21 children who had achieved clinical and histological remission with SFED, cow's milk was the most common food triggering disease recurrence (81%) followed by soy (19%) and wheat (14%) of patients based on data presented by Shah et al during an oral session at the Children's Digestive Health and Nutrition Foundation (CDHNF) Annual Meeting in San Diego, CA on November 14, 2008.

Food Substitutions and Cross-contamination in Elimination Diets

Directed and non-directed food elimination diets require more than the physician just directing the patient to eliminate the food(s) in question. Multiple concerns are raised including the fact that eliminating major foods such as milk, soy, wheat and egg from the diet of a growing child may have deleterious consequences. The foods removed should be adequately substituted to ensure the diet is nutritionally complete. This requires knowledge and understanding of the nutrient deficiencies caused by elimination of specific food as well the appropriate substitution for that food as shown in **Table 3**.

Another important aspect of eliminating foods from the diet involves food cross-contamination. Cross-contamination can transform a naturally occurring antigen-free food, into an antigen-containing food. Cross-contamination can occur during processing,

preparing, cooking or serving food. Many processed foods as well as fast foods may be cross-contaminated with one or more foods such as milk, soy, wheat or nuts. Cross-contamination can also occur during the process of food preparation at home and can be avoided by simple measures such as using different utensils and strict hand washing between cooking different foods. Tips for avoiding cross-contamination are summarized in **Table 4**.

Individuals on elimination diets must read food labels to ensure that those products are allowed in the diet. Food labels should be reviewed each time the product is consumed, because manufacturing or processing may have changed and a food that was formerly antigen-free, and may now contain the excluded antigen. The US Food and Drug Administration Food Allergen Labeling and Consumer Protection Act (FALCA) of 2004, has helped consumers identify foods that are potential allergens and if cross-contamination is a concern. This act requires that all foods made with any of the eight most common food allergens (cow milk, soy, egg, wheat, peanut, tree nut, fish and shellfish) must be clearly labeled to indicate the presence of these ingredients.¹²

Nutritional Assessment

Nutritional assessment of children with EoE, by a registered dietitian, prior to initiating the elimination diet is warranted. This assessment involves obtaining a detailed nutritional history including descriptions of food and supplements being consumed (including brand names of foods), preparation methods and eating environment, to improve compliance of prescribed nutritional therapy. Although, not very common, some

children may present with malnutrition. This is typically seen in younger children whose symptoms may include vomiting and food aversion or children with multiple IgE-mediated food allergies. The initial assessment may identify preexisting nutritional deficiencies which can be addressed concurrently when prescribing an elimination diet. Children who are on elimination diets for a prolonged period will need to have their nutritional intake monitored. In addition to anthropometric measurements including weight, height and body mass index (BMI), some children, especially those who have a large number of foods excluded, will require biochemical tests including complete blood count, pre-albumin, iron, calcium, and vitamin D levels to monitor for deficiencies.^{13,14}

Potential Nutritional and Other Consequences of Elimination Diets

It is important to be cautious when recommending elimination diets, since exclusion of important food elements from a growing child's diet can have disastrous consequences including impaired growth, rickets, and vitamin deficiencies.^{15,16} Kwashiorkor from protein-calorie-malnutrition has recently been reported in children on elimination diet when only milk protein was excluded from the diet of toddlers suspected of milk protein allergy.¹⁷ Frequently it is not a specific food per se that is a cause of nutritional deficiency as is the concurrent exclusion of a large number of processed foods that may contain that particular food antigen as a contaminant. Elimination diets with emphasis on excluding milk, wheat, soy and nuts amongst other foods also can be challenging for children on a vegan diet. Participation of a registered dietitian is extremely important to ensure a calorically adequate diet for growth, to provide education on appropriate food

substitutions, prevent contamination with excluded food antigens and to be an ongoing resource for families as they learn to adapt to the diet modification. Tips for successful elimination diet are shown in **Table 5**.

Other issues related to elimination diet include behavioral problems including refusal to comply with the diet since some of the younger children in daycare or elementary school settings do not want to appear or seem different from their peers. This, in our unpublished experience, has been a cause of treatment non-compliance. Depression, cheating, lying and stealing foods from other children are other behavioral consequences of diet therapy that have been reported in children on elimination diets for celiac disease and presumed food induced severe eczema. Proper patient selection for elimination dietary therapy can minimize these consequences.

Summary

Elimination of food proteins that are triggering esophageal inflammation often leads to resolution of symptoms and sustained healing of the esophagus. This treatment approach of eliminating the cause of esophageal damage is a logical cause and effect way to managing EoE. However, the different dietary treatments can be challenging and are often difficult to implement. Elemental diet with complete elimination of all intact food antigens offers the best outcome results as well as most complete healing but subsequent food reintroduction is long, tedious and often frustrating. Directed and standard or non-directed dietary treatments are less effective than elemental diet; both options offer good outcomes but directed elimination diet has the drawback that patch testing remains to be

validated and is not universally available. When contemplating dietary options it is important to remember that one size does not fit all and that dietary approach needs to be tailored to the needs of the individual patient.

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Table 1
Outcome of Various Dietary Approaches in Eosinophilic Esophagitis

Author	No.	Allergy Tests	Diet	Outcome	Residual Eosinophil Count
Kelly ¹	10	SPT 6/9	Elemental diet	Clin. impr. 10/10 (100%) Histologic impr: 9/10 (90%)	0.5
Teitelbaum ⁹	11	SPT/ RAST	Allergy test Based elimination	No improvement	
Noel ¹⁰	10	SPT	Elimination diet	No response	
Spergel ⁶	146	SPT & APT	Elimination diet	Significant impr: 112 (77%) Partial impr: 19 (13%) Treatment failure 15 (10%)	1.1 \pm 2.1 12.0 \pm 3.2 36.3 \pm 14.9
Laicouras ³	172		Elemental diet	Significant clinical & histologic improvement 160/164 (98%)	1.1 \pm 0.6
Kagalwalla ⁴	60 ELED 25 SFED 35	Allergy tests not utilized	SFED Elemental diet	Sig impr SFED = 26/35 (74%) Sig impr ELED = 22/25 (88%)	3.1 \pm 3.2 1.6 \pm 2.1
Gonsalves ⁷	18		SFED	Significant clinical & histologic improvement 14/18 (78%)	

Table 2

Dietary introduction approach to food re-introduction in Eosinophilic Esophagitis

<div> <div>Start</div> <div>—————→</div> <div>End</div> </div> <div> <div>(Least Allergenic)</div> <div>(Most Allergenic)</div> </div>			
A	B	C	D
Vegetables (non-legume) Carrots, squash (all types), sweet potato, white potato, string beans, broccoli, lettuce, beets, asparagus, cauliflower, brussel sprouts, Fruit (non-citrus, non- tropical): Apple, pear, peaches, plum, apricot, nectarine, grape, raisins Vegetables Tomatoes, celery, cucumber, onion, garlic, any other vegetables	Citrus Fruits Orange, grapefruit, lemon, lime Tropical fruits Banana, kiwi, pineapple, mango, papaya, guava, avocado Melons Honeydew, cantaloupe, watermelon Berries Strawberry, blueberry, raspberry, cherry Cranberry Grains Rice, millet, quinoa	Legumes Lima beans, Chickpeas, white/black/red beans Grains Oat, barley, rye, other grains Meat* Lamb, chicken, turkey, pork *progress from well-cooked to rarer	Fish/Shellfish Corn Peas Peanut Wheat Beef Soy Egg Milk

* Modified with permission from Table 2 published by Spergel et al⁶

Table 3
Potential Nutritional Deficiencies

Food	Nutrients	Alternative Food Sources
Milk	Protein, Calcium, Vitamin D, Vitamin A, B12, Riboflavin, Pantothenic acid, Potassium	Meats, legumes, whole grains, nuts, fortified foods (with B vitamins, calcium, vitamin D)
Egg	Protein, Vitamin B12, Pantothenic acid, Biotin, Selenium	Meat, chicken, legumes whole grains
Soy	Protein, Iron, Zinc, Magnesium, Thiamin, Riboflavin, Pyridoxine, Folate	Meats, allowed grains
Wheat	Iron, Thiamin, Riboflavin, Niacin, Folic acid	Alternative grains that are fortified
Peanut/Tree Nut	Vitamin E, Niacin, Magnesium, Manganese, Chromium, Folic Acid, B6, Copper, Zinc, Selenium, Phosphorus, Potassium	Legumes, whole grains, vegetable oils
Fish/Shellfish	Vitamin E, B6, Niacin, Phosphorus, Selenium, Omega 3 fatty acids	Whole grains, meats, soybean, flaxseed, nuts, oils

Table 4

Tips Avoid Cross-Contamination

- Follow proper hand-washing procedures
- Prepare antigen free foods first, then cover
- Clean surfaces and utensils before/after preparing antigen-free foods
- Separate antigen-free from antigen-containing foods
- Seal or wrap antigen-free foods
- Separate condiments (to avoid double dipping) or use squeeze bottles/sprays

Table 5
Tips for Successful Elimination Diet

Problem	Potential Solution
Unfamiliar foods	Involve child in preparation, serve variety of safe foods using different preparations, safe spices for different tastes
Cooking	Food Allergy and Anaphylaxis Network (FAAN) cookbooks, newsletters, online, cooking shows/cooking magazines-adapt ideas to special foods
Eating out/socialization	Have plan, call ahead to restaurants, go off peak times, talk to chef/manager. Bring own food if unable to meet needs.
Traveling	Bring own food staples, if possible stay in hotel with kitchenette, call hotel, restaurants ahead regarding dietary restrictions.
Holidays/birthday party	Plan gatherings around non-meal times, have non-food related activities, i.e. “non-cake” cake
Sneaking foods	Make sure child understands consequences—cheating can cause harm to body. Let EoE team know so can postpone Endoscopy.
Other caregivers/relatives	Provide a written explanation of what EoE is & what the diet is. Provide list of acceptable and unacceptable foods. Consider providing snacks/meals when outside home.